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Laboratory investigation and clinical outcomes in sickle cell disease patients infected with COVID-19: A single-center experience in India

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ABSTRACT

Background: Patients with sickle cell disease (SCD) have been part of the population 'high-risk' group since the COVID-19 pandemic. This study focused to understand impact ofCOVID-19 on clinical outcomes in SCD. *Methods*: Data were taken at the baseline and clinical course of this prospective one-center intervention in SCD patients diagnosed with COVID-19 in isolation centers (associated with Sevagram Hospital) dedicated for COVID-19 patients in Wardha, Maharashtra, India. Patients were followed-up post-hospital discharge for up to 1 month. *Results*: Of 120 SCD patients with COVID-19, 88 patients (73.33%) required hospitalization, and 32 died (26.67%). Vasocclusive pain was the most common symptom. In 36.36% of hospitalised people and all those who died, acute chest syndrome occurred. Older and recent hypertension records, congestion and stroke, and elevated levels of creatinine and bilirubin were common among patients who died. *Conclusion*: The risk for morbidity, including ACS, seems the greatest among older patients with sickle cell status, particularly those who have chronic end-organ diseases, including brain, heart and lung.

Keywords: COVID-19, Sickle cell disease, India, Hematology

1. INTRODUCTION

Historically, coronaviruses have been a causative agent for serious human diseases (He & Deng, 2020; Hon et al., 2020). The novel coronavirus disease (COVID-19) has already affected over 6.9 million people, claiming more than 400000 lives in over 200 nations all over the world (Lippi & Plebani, 2020). India reported the first laboratory-confirmed case of COVID-19 on 30 January 2020 in the state of Kerala (Andrews et al., 2020). There have been nearly 3.5 million COVID-19 cases in India since 15 February 2021 (Patrikar et al., 2020). Sickle cell disease and Sickle cell trait are a hereditary hemoglobin disorder (Kato et al., 2018). In the tribals in Nilgiri Hills of southern India in 1952 the presence of sickle hemoglobin was first identified in India (Colah et

al., 2015). Several studies have shown that SCD is a major health burden in India (Sinha et al., 2015). In Maharashtra, the gene is common in all the eastern parts of Satpura in the North and in some parts of Marathawada, also called Vidarbha province (Buktar et al., 2018). In various tribes, the frequency of sickle cell carrier ranges from 0 to 35% (Sheshadri et al., 2021).

Vasoocclusion is marked by an irregular red blood vessel, white blood cells and platelets, which contribute to both acute and chronic pain and a wide variety of symptoms involving any organ system which may cause organ injury, reduced quality of life and damage to the organ itself. Moreover, SCD patients survive less than the general population for decades (Vercellott et al., 2019; Nur et al., 2020). The SCD population is especially vulnerable to global viral pandemics, as shown by increasingly demanding acute treatment, including invasive ventilation and interchangeable transfusions in patients with SCD (Sahu & Cerny, 2020). During the research, we estimated that the risk of morbidity and mortality due to COVID-19 infection is higher in patients with SCD. The elevated risk will probably be etiological multifactorial, with causes that range from SCD related immune impairments. All these factors would increase their probability of hospitalization or death (Panepinto et al., 2020).

This research aimed at understanding the effect of COVID-19 on clinical conditions in SCD patients and to inform better treatment and treatment practices in the patients' cohortage.

2. METHODS

Study population

Study was conducted at Life Wave Diagnostic and Research Centre, Mumbai, Maharashtra, India. Study population comprised 120 adult patients living with SCD/SCT and they were diagnosed and admitted due to COVID-19. Only symptomatic patients were included and those on any antioxidant supplements were excluded. Rapid antigen testing (RAT) was used to screen COVID-19 patients. Patients with SCD/SCT and COVID-19 infection were confirmed by results of reverse-transcriptase polymerase chain reaction (RT-PCR) testing of nasopharyngeal samples between 10 November 2020 and 10 February 2021 was included. All the patients were followed-up clinically after diagnosis for upto 1 month. No patients had been omitted from testing, and no follow-up patients had been missed.

Data collection

Collection of data for this comparative study was undertaken from one of the isolation centers (associated with Sevagram Hospital) dedicated for COVID-19 patients in Wardha, Maharashtra, India. To maintain homogeneity of the data, we collected all the data from single isolation center only. Our institutional evaluation committee has adopted the compilation of data as the minimum risk research and collected information from all participants in the report.

In patients with COVID-19 infections, clinical data were gathered prospectively using a structured form for electronic medical records in the specialist isolation center. Demographic, psychiatric history and use of medicines, key evidence before and during the presence of hospitalization, clinical testing during the hospitalization, hospital procedures and therapies and results were gathered from all the patients. Data from their first hospitalization was provided for patients hospitalised more than once during the research time.

Statistical analysis

Data were reported by using mean, percentage and frequency tables. Variables were measured to those hospitalized patients and those who did not use a Student T-test. All analyses were performed in SPSS version 16. P-value of ≤0.05 was considered to be statistically significant.

3. RESULTS

The demographic and clinical features of 120 patients are addressed in table 1. The age range was 18 years months to 62 years; the mean age was 37.3 years. Majority of study participants were male (60%). Roughly 60% had SCD while rest had SCT which was common for western Maharashtra distribution. The most frequent comorbidity has been seen in 14 patients with hypertension. This was followed by diabetes which was recorded in 48 patients (40%). Forty four patients (36.67%) experienced stroke. Majority of the patients under went chronic transfusion (73.33%). Sixty eight (56.67%) patients were treated with one SCD-specific therapy, which was primarily hydroxyurea (HU).

Table 1 Pre-infection characteristics of the study population

	All patients		Not-hospitalized		Hospitalized	
Characteristic	n	Results [n (%)]	n	Results [n (%)]	n	Results [n (%)]
Demographics						
Age (Years)	120	37.3	32	35.8	88	39.5
Gender Male Female	120	 72 (60) 48 (40)	32	 20 (62.5) 12 (37.5)	88	 52 (59.09) 36 (40.91)
Sickle cell status SCT SCD	120	 48 (40) 72 (60)	32	 20 (62.5) 12 (37.5)	88	 48 (54.55) 40 (45.45)
BMI (kg/m^2)	120	24.3	32	24.2	88	23.9
Medical history						
Diabetes	120	48 (40)	32	4 (12.5)	88	60 (68.18)
Hypertension	120	56 (46.67)	32	8 (25)	88	72 (81.82)
Stroke	120	44 (36.67)	32	4 (12.5)	88	36 (40.91)
ACS	120	36 (30)	32	4 (12.5)	88	32 (36.36)
CHF	120	20 (16.67)	32	8 (25)	8	28 (31.82)
Treatment						
Chronic transfusion	120	88 (73.33)	32	28 (87.5)	88	48 (54.55)
Hydroxyurea	120	68 (56.67)	32	24 (75)	88	52 (59.09)

Table 2 Clinical features of the study participants during COVID-19 infection

	All patients		Not-hospitalized		Hospitalized	
Presenting condition	n	Results [n (%)]	n	Results [n (%)]	n	Results [n (%)]
Vaso-occlusive Pain	120	104 (86.67)	32	28 (87.50)	88	76 (86.36)
Acute chest syndrome	120	76 (63.33)	32	24 (75)	88	52 (59.09)
Temperature (≥38°C)	120	68 (56.67)	32	0 (0)	88	68 (77.27)
Heart rate (>100 bpm)	120	60 (50)	32	4 (12.5)	88	56 (63.64)
Oxygen saturation (<92% on room air)	120	36 (30)	32	4 (12.5)	88	32 (36.36)

Table 3 Tabulated laboratory values of hospitalized and not hospitalized patients during infection

	Not hospitalized					Hospitalized				
	Baseline		Presentation			Baseline		Presentation		
Variable	n	Results	n	Results	P	n	Results	n	Results	P
Hemoglobin (g/dL)	32	9.1	32	8.2	0.35	88	8.8	88	7.9	0.04
W.B.C (cell/mcl)	32	8.2	32	9.6	0.77	88	10.2	88	11.8	0.14
Platelet count (cell/mcl)	32	339	32	356	0.91	88	314	88	309	0.13
Lymphocyte count (cell/mcl)	32	2.7	32	2.4	0.26	88	2.5	88	2.3	0.12
Neutrophil count (cell/mcl)	32	4.7	32	4.9	0.55	88	5.1	88	5.4	0.10
Creatinine (mg/dL)	32	0.7	32	0.72	0.05	88	0.81	88	0.89	0.04
Bilirubin (mg/dL)	32	1.91	32	1.82	0.33	88	1.95	88	1.82	0.21
C-reactive protein (mg/L)	32	0.7	32	3.2	0.05	88	1.9	88	13.6	0.03

Table 2 and Table 3 involved the clinical and hematological characteristics of hospitalized patients compared with non-hospitalized patients. Over all, 88 (73.33%) of 120 patients required hospitalization. There was no difference between unhospitalized and hospitalised patients from the sickle-celled status and patient age. In hospitalized patients hypertension was more common than in non-hospitalized patients (72 of 88 [81.82%] vs 56 of 120 [46.67%]). The most frequent symptom of COVID-19 in SCD and

SCT patients was vaso-occlusive discomfort. In all SCD patients who were infected with COVID–19, fever, characterized by a temperature of 38°C was normal at the first presentation. Tachycardia occurred in 60 (50%) of 120 patients at presentation. Hypoxia in 30% of the patients was initially found.

Patients who were hospitalized had a significantly lower hemoglobin count than compared with not-hospitalized patients ($p<0.05$). The levels of creatinine and C-reactive protein were also recorded significantly higher in hospitalized patients as compared to non-hospitalized patients. In addition, in comparison with its stationary values before COVID 19 infection, this report detailed the laboratory results for both hospitalized and non-hospital patient presentations (Tables 2 and 3). This research found that non-hospitalised patients had minor variations in their hematological parameters such as hemoglobin counts, WBCs, platelets and lymphocytes.

Hemolysis markers like Bilirubin did not vary substantially in hospitalization patients from baselines. This indicated that hemolysis was not of major importance in COVID-19 patients and that a decrease in hemoglobin found in hospital patients was most likely secondary to the abolition of bone marrow. The serum creatinine and a C-reactive steady protein were statistically significantly increased in inpatients.

Table 4 Demographic and clinical factors for patients who died in hospital

	Alive		Death		
Variable	n	Results [n (%)]	n	Results [n (%)]	P
Age	56	31.2	32	36.3	0.05
Gender Male Female	56	 44 (78.57) 12 (21.43)	32	 24 (75) 8 (25)	 0.45 0.67
Sickle cell status SCD SCT	56	 40 (71.43) 16 (28.57)	32	 20 (62.50) 12 (37.30)	 0.72 0.77
BMI (kg/m^2)	56	23.9	32	24.2	0.89
Medical History					
Diabetes	56	44 (78.57)	32	28 (87.50)	0.33
Hypertension	56	48 (85.71)	32	28 (87.50)	0.05
Stroke	56	52 (92.86)	32	24 (75)	0.01
ACS	56	44 (78.57)	32	32 (100)	0.45
CHF	56	52 (92.86)	28	24 (75)	0.02
Presenting condition					
Vaso-occlusive Pain	56	36 (64.29)	32	28 (87.50)	0.04
Acute chest syndrome	56	20 (35.71)	32	28 (87.50)	0.49
Temperature (≥38°C)	56	32 (57.14)	32	24 (75)	0.51
Heart rate (>100 bpm)	56	44 (78.57)	32	32 (100)	0.91
Oxygen saturation (<92% on room air)	56	36 (64.29)	28	24 (75)	0.97
Presenting laboratory tests					
Hemoglobin (g/dL)	56	8.5	32	5.7	0.08
W.B.C (cell/mcl)	56	11.2	32	11.7	0.10
Platelet count (cell/mcl)	56	323	32	274	0.11
Lymphocyte count (cell/mcl)	56	2.3	32	2.3	0.07
Neutrophil count (cell/mcl)	56	5.2	32	5.4	0.22
Creatinine (mg/dL)	56	0.7	32	4.4	0.05
Bilirubin (mg/dL)	56	1.96	32	1.67	0.17
C-reactive protein (mg/L)	56	11.5	32	29.6	0.45
Treatment during hospitalization					
Chronic transfusion	56	48 (85.71)	32	20 (62.50)	0.33
Hydroxyurea	56	36 (64.29)	32	16 (50)	0.28

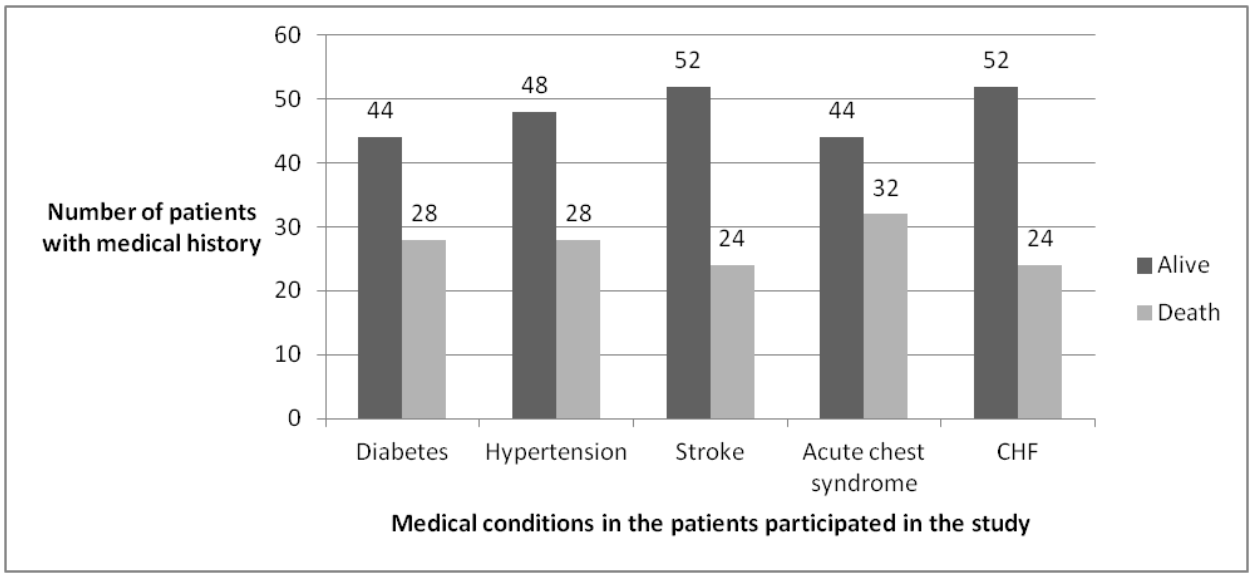

Figure 1 Number of patients with medical history.

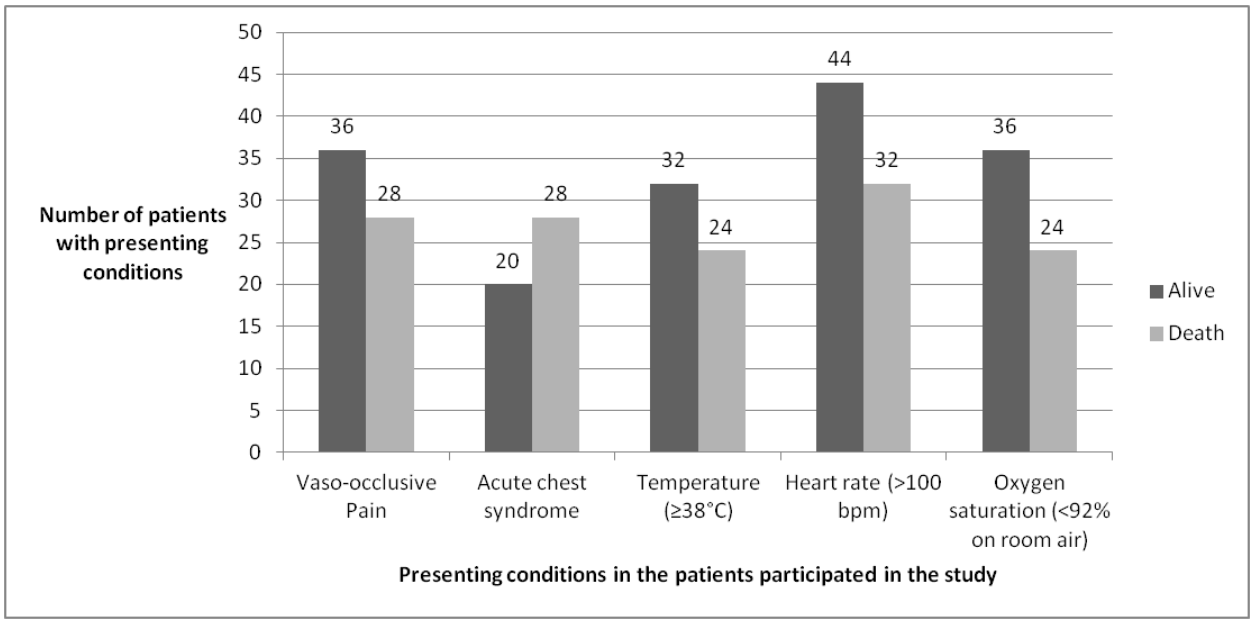

Figure 2 Number of patients with presenting conditions.

We recorded thirty two deaths (20 of SCD and 12 of SCT) before 15 Feb 2021 in our cohort (Table 4), for a total death rate of 26.67%. The average age is 36.3, less than the average age of the whole cohort of 37.3 years, and 75% are men. In these patients, the percentage of basic hypertension, stroke and CHF was statistically significantly greater. Vaso-occlusive pain was more common in people who died (p=0.04). ACS was reported in every patient who died. Laboratory values at presentation revealed that those who died had higher levels of C - reactive protein and creatinine than those who survived (Table 4, figure 1 & 2). Figure 3 illustrated the chest radiographic images of six sickle cell disease patients who were infected with COVID-19 and died. Remaining chest radiographic images of sickle cell disease patients infected with COVID-19 could not be obtained.

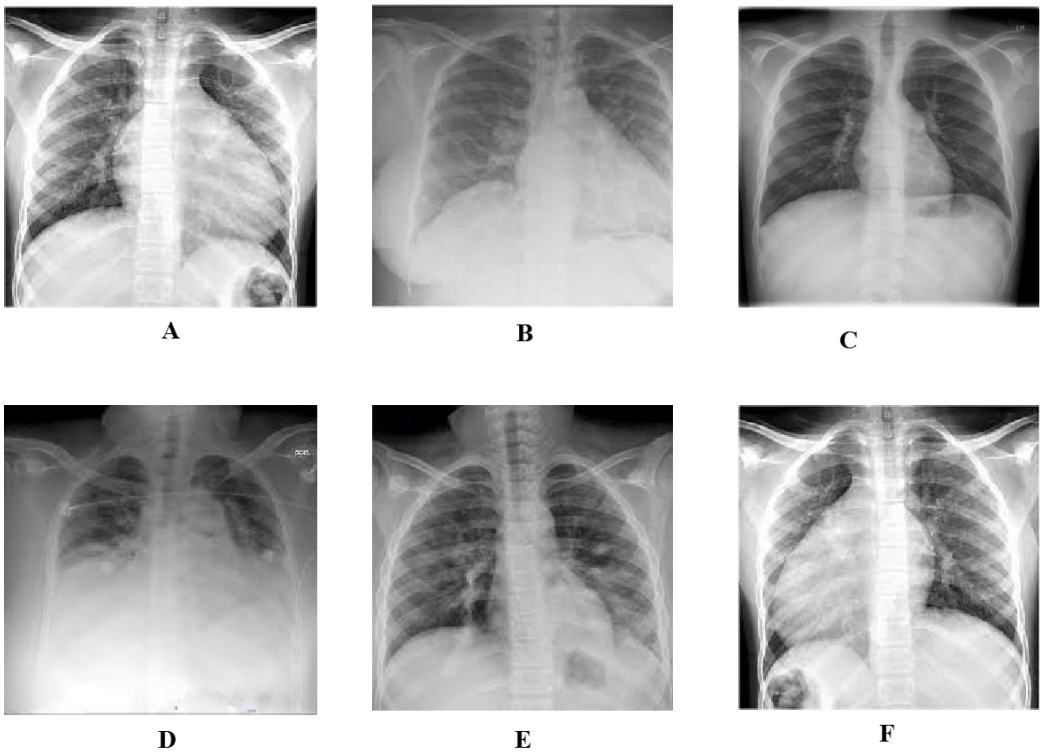

Figure 3 Chest radiographic images of six sickle cell disease patients who were infected with COVID-19 and died.

4. DISCUSSION

Our analysis augmented important clinical data on clinical path and survival factors in SCT/SCD and COVID-19 infected patients. Our cohort included consecutively identified COVID-19–infected patients with SCT/SCD at a dedicated isolation centers (associated with Sevagram Hospital) for COVID-19 patients in Wardha, Maharashtra, India. Several written documents also included reports of the clinical features and death rates of SCD and COVID-19 patients (Hussain et al., 2020; McCloskey et al., 2020; Chakravorty et al., 2020). Seven percent of the deaths in 178 patients were registered in the US register, while the French cohort had two deaths in 83 (Panepinto et al., 2020).

In our sample the mortality rate was 26.67 percent, higher than in the previously reported SCD cohorts (Hussain et al., 2020; Mc Closkey et al., 2020; Chakravorty et al., 2020; Panepinto et al., 2020). Since we were only mindful of patients that were symptomatic and who were presenting in healthcare system, the fats in the SCD may be less than most current literatures. We are not able to conclude that COVID-19 was the nearest cause of death among the patients who were deceased but we have included these deaths since they could be late in the after math of COVID-19. Our results show the relevance of close follow-up of all COVID-19 SCD cases, even though the original infection led to mild illnesses.

The present cohort has raised the risk of mortality by older ages and the prevalence of end-organ diseases, in particular lung hypertension. We found that serious COVID-19 infections and death was not restricted only to SCD in accordance with other cohorts. Similarly, people with SCT were affected and portrayed between people in hospital and deceased. More commonly, severe hospitalization disorder has arisen in those with pre-existing brain, renal, cardiac and lung disease that reflects systemic blood vasculitis. This indicates that multiple end-organ patients, particularly hypertension and CHF, should be actively assessed and handled in the context of COVID-19 infection regardless of sickle cell state. Vaso-occlusive pain was the most frequent characteristic of this demographic and physicians were expected to receive COVID-19 tests. We observed that, in contrast to the H1N1 patients with SCD, there was no association with severe hemolysis with COVID-19 infection. Hydroxyurea may have a beneficial effect on reducing hemolytic diseases, plateles and leucocytes. HU will directly beneficially impact microvasculature independently of the fetal hemoglobin-elevating properties of the medicine (Guarda et al., 2019).

SCD is an impaired survival disorder (De Baun et al., 2019). Our median age was even less than the age of the Indian non-SCD population for the people who died of COVID-19 infection (62.5 years). We cannot definitely tell if the total death rate of a patient with SCD is higher because of the limited sample limitations. We begin to realize the clinical characteristics that put people with

SCD at a greater risk of hospitalization and death. Older patients, irrespective of the genotype of hemoglobin, particularly those with chronic end-organ disease, appear to be at most high risk of morbidity, like ACS. The highest chances of death by COVID-19 in patients are with SCD Hypertension. We must validate our results in greater cohorts, but hopes they will help stratify SCD patients while this pandemic progresses.

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We thank the participants who all contributed samples to the study.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in thestudy. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical Consideration

The study acquired the ethical approval from the ethical committee at the LifeWave Diagnostic and Research Center (letter number 8611/2018).

Author Contributions

Corresponding author contributed for data collecting, analysis and drafting the manuscript. Second author contributed towards proofreading the final draft.

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Conflict of Interest

There are no conflicts of interest.

Data and materials availability

All data associated with this study are present in the paper.

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